STUDIES ON CONDENSED-HETEROCYCLIC AZOLIUM CEPHALOSPORINS

I†. SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 7β-[2-(2-AMINOTHIAZOL-4-YL)-2(Z)-ALKOXYIMINOACETAMIDO]-3-(IMIDAZO[1,2-a]PYRIDINIUM-1-YL)METHYL-3-CEPHEM-4-CARBOXYLATES

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In our study of the structure-activity relationships of cephalosporins bearing quaternary ammonium groups at the 3 position, we postulated that delocalization of the azolium positive charge would lead to an expanded antibacterial spectrum and increased activity. Since quaternization of condensed-heterocyclic compounds such as imidazo[1,2-*a*]pyridine gives positive charge delocalization, 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]cephalosporin derivatives (**1**~**53**) bearing various (imidazo[1,2-*a*]pyridinium-1-yl)methyl moieties at the 3 position were prepared and their antibacterial activity was determined. As expected, these cephalosporins exhibited potent activity against both Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*. These results imply that imidazo[1,2-*a*]pyridine is a quite useful substituent for improving antibacterial activity and spectrum. The structure-activity studies revealed that a favorable substituent on the imidazo[1,2-*a*]pyridine is the cyano radical at the 6 position of the ring, and ethoxyimino or 1-carboxy-1-methylethoxyimino groups are suitable for the alkoxyimino substituent. Among the cephalosporins tested, 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-ethoxyiminoacetamido]-3-(6-cyanoimidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**45**) and 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-(1-carboxy-1-methylethoxyiminoacetamido]-3-(6-cyanoimidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**49**) showed good antibacterial activity.

In recent years, a number of cephalosporin antibiotics with a broad spectrum of activity and increased resistance to β-lactamases have been prepared[2]. Most of them have a 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido] group at the 7 position of the cephem nucleus, such as cefmenoxime (CMX) and ceftazidime (CAZ), and their antibacterial activity against *Staphylococcus aureus* and other Gram-positive bacteria is inferior to that against *Escherichia coli*, *Klebsiella pneumoniae* and other Gram-negative bacteria. Since these so-called third generation cephalosporins have been applied in clinical practice, the incidence of infection caused by Gram-positive bacteria including methicillin-resistant *S. aureus* (MRSA) has been increasing[3].

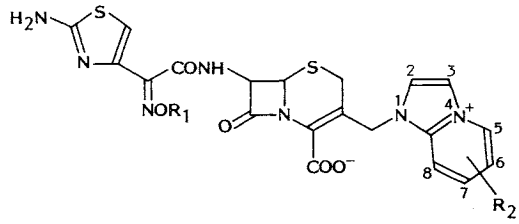
Recently, cephalosporins bearing a quaternary ammonium methyl group at the 3 position, such as cefpirome (CPR)[4,5] and cefepime (CFPM)[6], have been prepared, and their activity against both Gram-positive and Gram-negative bacteria is superior to that of the third generation cephalosporins. We assumed that these cephalosporins showed potent activity against Gram-negative bacteria including *Pseudomonas aeruginosa* because the hydrophilic structure and zwitterionic form allow them to pass through

† Part of this paper was presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy[1].

the outer membrane of Gram-negative bacteria. However, this would not explain the potent activity against Gram-positive bacteria which do not have the outer membrane.

Thus, we turned our focus to the relationship between permeability and the quaternary ammonium moiety of the cephalosporins. We postulated that if a positive charge at the 3 position in the moiety could be delocalized, the polarity of the molecule could be reduced, and the cephalosporins would show activity against both Gram-positive and Gram-negative bacteria including *P. aeruginosa*. From these reasons, we became interested in imidazo[1,2-*a*]pyridine, whose quaternization leads to delocalization of the positive charge over the whole ring.

Fig. 1. Structure of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(substituted imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**I**).



Moreover, the results of charge distribution of 1-methylimidazo[1,2-*a*]pyridinium iodide calculated using the modified neglect of differential overlap (MNDO) method (TAKAMOTO; personal communication) imply that the positive charge delocalizes over the ring and that the bridged head nitrogen shows a more positive charge than the other nitrogen.

These speculations prompted us to prepare a new series of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]cephalosporins bearing an imidazo[1,2-*a*]pyridiniummethyl group at the 3 position.

In this report, we describe the synthesis and antibacterial activity of new cephalosporins represented by formula **I** (Fig. 1).

Chemistry

The 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(substituted imidazo[1,2-*a*]pyridinium)methyl cephalosporins (**1**~**53**) were prepared by the substitution of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acids (**Va**~**Vp**, **XIIa**~**XIId**) with various substituted imidazo[1,2-*a*]pyridines (**XIII**).

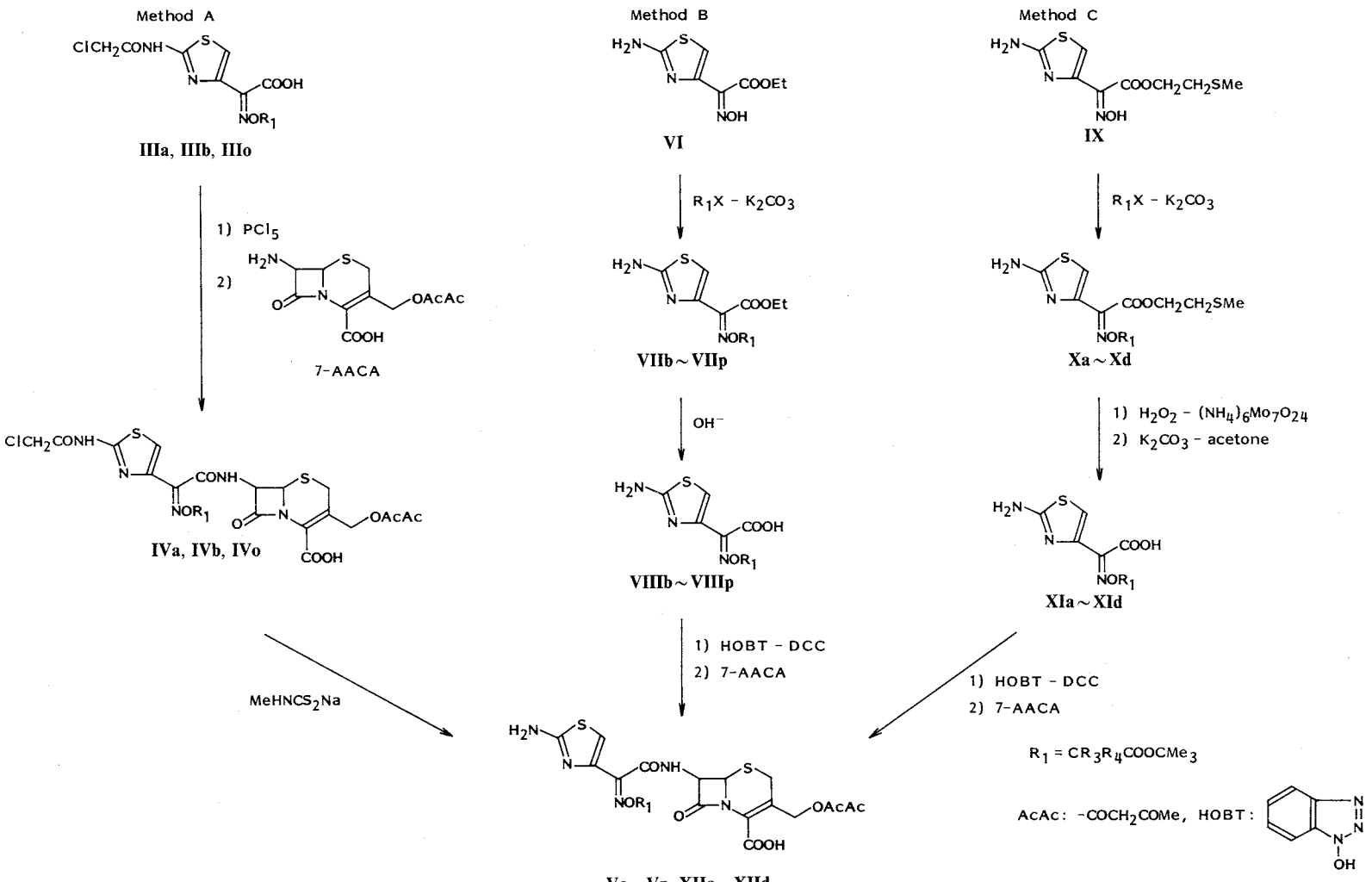
The starting materials, 2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetic acid derivatives (**III**, **VIII**, **XI**), were prepared by three methods, according to the differences in alkyl groups (R_1), as shown in Scheme 1.

2-(2-Chloroacetamidothiazol-4-yl)-2(*Z*)-alkoxyiminoacetic acids (**IIIa**, **IIIb**, **IIIo**) with an R_1 of less hindered alkyl groups such as methyl, ethyl and carbamoylmethyl were prepared according to the procedure of OCHIAI *et al.*[7] (Method A).

VIII derivatives with an R_1 of other alkyl groups were prepared following the procedure mentioned below. Ethyl 2-(2-aminothiazol-4-yl)-2(*Z*)-hydroxyiminoacetate (**VI**) was reacted with excess alkyl halide in the presence of potassium carbonate in acetone to give ethyl 2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetate (**VII**). **VIII** was obtained by alkaline hydrolysis of **VII** (Method B).

Preparation of **XI** with an R_1 of a carboxyalkyl group was attempted following Method B, but the ethyl ester moiety of **VII** was not hydrolyzed regioselectively except in the case of ethyl 2-(2-aminothiazol-4-yl)-2(*Z*)-1-*tert*-butoxycarbonyl-1-methylethoxyiminoacetate. Thus, according to the procedure of TAKANOHASHI[8], methylthioethyl 2-(2-aminothiazol-4-yl)-2(*Z*)-hydroxyiminoacetate (**IX**) was treated with *tert*-butyl 1-bromoalkylcarboxylate to afford methylthioethyl 2-(2-aminothiazol-4-yl)-2(*Z*)-(1-*tert*-butoxycarbonylalkoxyimino)acetate (**X**). **X** was treated with ammonium molybdate in acetone,

Scheme 1.


Method A
ClCH2CONH
COOH
NOR1
IIIa, IIIb, IIIo
1) PCl5
2)
H2N
OAcAc
COOH
7-AACA
ClCH2CONH
CONH
NOR1
OAcAc
COOH
IVa, IVb, IVo
MeHNCS2Na
Method B
H2N
COOEt
NOH
VI
R1X - K2CO3
H2N
COOEt
NOR1
VIIb~VIIp
OH−
H2N
COOH
NOR1
VIIIb~VIIIp
1) HOBT - DCC
2) 7-AACA
H2N
CONH
NOR1
OAcAc
COOH
Va~Vp, XIIa~XIId
Method C
H2N
COOCH2CH2SMe
NOH
IX
R1X - K2CO3
H2N
COOCH2CH2SMe
NOR1
Xa~Xd
1) H2O2 - (NH4)6Mo7O24
2) K2CO3 - acetone
H2N
COOH
NOR1
XIa~XId
1) HOBT - DCC
2) 7-AACA
R1 = CR3R4COOCMe3
AcAc: -COCH2COMe, HOBT:
N
N
N
OH

followed by the oxidation with hydrogen peroxide to give its methylsulfinyl ester. **XI** was obtained by the hydrolysis of the methylsulfinyl ester (Method C).

The condensation of the acids **III**, **VIII** and **XI** with 7β-amino-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (7-AACA) is shown in Scheme 1.

III was reacted with PCl_5 to give the acid chloride, which was condensed with 7-AACA in the presence of sodium hydrogen carbonate to give 7β-[2-(2-chloroacetamidothiazol-4-yl)-2(*Z*)-methoxy- and ethoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acids (**IVa**, **IVb**). **IV** was deprotected with sodium *N*-methyldithiocarbamate to afford 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxy- and ethoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acids (**Va**, **Vb**).

VIII and **XI** were treated with 1-hydroxybenzotriazole (HOBT) in the presence of *N*,*N*-dicyclohexylcarbodiimide to give the HOBT esters of **VIII** and **XI**, which reacted with 7-AACA in the presence of triethylamine to afford 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acids (**Vb**$\sim$**Vp**, **XIIa**$\sim$**XIId**).

The known imidazo[1,2-*a*]pyridines (**XIII**) were prepared following the procedure described in the literature[9~17]. 5-Methylthioimidazo[1,2-*a*]pyridine (**XIIIk**) was afforded by the substitution of 5-chloroimidazo[1,2-*a*]pyridine (**XIIIl**) with sodium methylthiolate in dimethylformamide. The other imidazo[1,2-*a*]pyridines such as 6-carbamoyl- (**XIIIn**), 6-fluoro- (**XIIIp**) and 8-fluoroimidazo[1,2-*a*]pyridine (**XIIIv**) were obtained by the reaction of the corresponding 2-aminopyridine derivatives with α-bromoacetaldehyde. 6-Cyanoimidazo[1,2-*a*]pyridine (**XIIIs**) was obtained by the dehydration of **XIIIn** with $POCl_3$.

The synthesis of 3-azoliummethyl cephalosporins (**1**$\sim$**53**) is outlined in Scheme 2. 7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**Va**$\sim$**Vp**) was heated with 3$\sim$6 equiv of imidazo[1,2-*a*]pyridine (**XIII**) and the same amount of potassium iodide in 50% aqueous acetonitrile at 60$\sim$70°C for 1$\sim$2 hours. The reaction mixture was purified by column chromatography on silica gel with acetone-water or acetonitrile-water as the eluent, followed by repurification by column chromatography on MCI gel CHP-20P or Amberlite XAD-2 to give the objective cephalosporins **1**$\sim$**16**, **21**$\sim$**43**, **45**$\sim$**48**, **50**, **52** and **53** in 1$\sim$22% yield (Method D).

In the case of cephalosporins **17**$\sim$**20**, **44**, **49**, and **51**, **XII** was reacted with **XIII** following a procedure similar to that described above and the product was deprotected with trifluoroacetic acid. The desired cephalosporins were isolated as the sodium salt by column chromatography on MCI gel CHP-20P (Method E).

Biological Results and Discussion

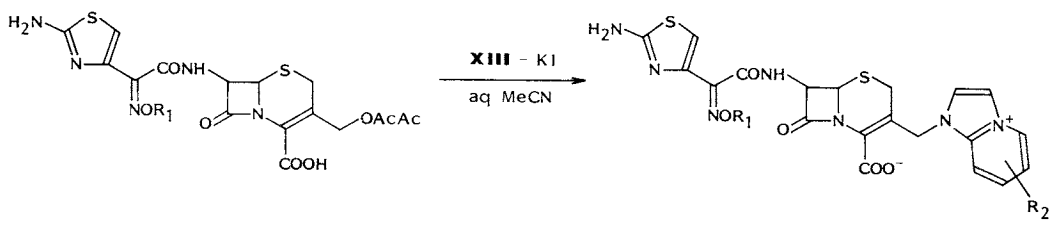
The MICs of the prepared cephalosporins **1**$\sim$**53** along with CMX and CAZ as reference compounds against selected organisms, *i.e.*, *S. aureus* 308A-1, *E. coli* NIHJ JC-2, *Enterobacter cloacae* IFO 12937, *Serratia marcescens* IFO 12648, *Proteus vulgaris* IFO 3988, *P. aeruginosa* IFO 3455 (β-lactam sensitive strain, *P.a.* 1) and *P. aeruginosa* U-31 (β-lactam resistant strain, *P.a.* 2) were determined by the standard serial 2-fold agar dilution method[18].

Table 1 summarizes the effect of the oxime substituent (R_1) in a series of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylates on the MIC.

Cephalosporins **1** and **2** with R_1 of a methyl or ethyl group showed potent antibacterial activity

Scheme 2.

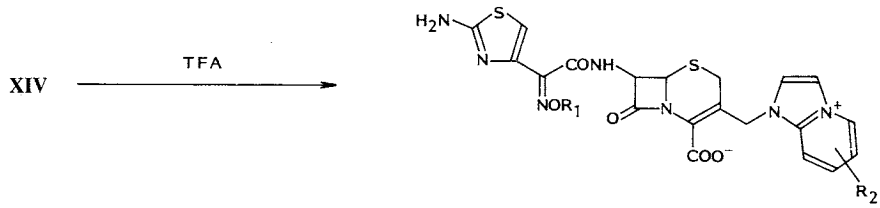
Method D



Va~Vp, XIIa~XIId

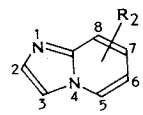
1~16, 21~43, 45~48, 50, 52, 53
XIV17~XIV20, 44, 49, 51
(XIV $R_1 = CR_3R_4CO_2CMe_3$)

Method E



17~20, 44, 49, 51 $R_1 = CR_3R_4CO_2Na$

XIII:



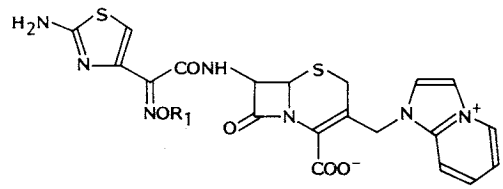
XIII	R_2	XIII	R_2
a	H	**l**	5-Cl
b	2-$CONH_2$	**m**	6-Me
c	2-CO_2H	**n**	6-$CONH_2$
d	2-CO_2Et	**o**	6-CO_2H
e	3-CH_2NMe_2	**p**	6-F
f	3-CH_2CN	**q**	6-Cl
g	3-C=NOH H	**r**	6-Br
		s	6-CN
h	3-CN	**t**	8-Me
i	5-Me	**u**	8-$OCH_2C_6H_5$
j	5-OMe	**v**	8-F
k	5-SMe		

against both Gram-positive and Gram-negative bacteria. The antibacterial activity of both **1** and **2** against *S. aureus* was superior to that of CAZ.

The antibacterial activity of cephalosporins **1~7** against *S. aureus* tended to be improved with increasing carbon numbers of R_1, whereas the activity against Gram-negative bacteria was decreased.

The MICs of cephalosporins **8~15** except the benzyl derivative **10** were similar to that of **1**. Of these, cephalosporins with an R_1 of 2-chloroethyl (**12**) and 2-hydroxyethyl (**13**) moieties showed improved activity against *S. aureus* and *P.a.* 1, but they did not show activity against highly resistant *P. aeruginosa* (*P.a.* 2).

Table 1. Antibacterial activity (MIC, μg/ml) of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylates (**1**～**20**).



Compound	R_1	*S.a.*	*E.c.*	*E.cl.*	*S.m.*	*P.v.*	*P.a.*1	*P.a.*2[a]
1	Me	0.39	<0.1	0.39	0.2	0.2	6.25	>100
2	Et	0.39	<0.1	0.78	0.2	0.2	3.13	100
3	*n*-Pr	0.2	0.78	1.56	1.56	1.56	6.25	100
4	*n*-Bu	0.2	3.13	6.25	6.25	6.25	25	>100
5	*n*-Hex	<0.1	6.25	6.25	6.25	6.25	25	100
6	C_5H_9 (cyclo-)	0.2	1.56	3.13	3.13	1.56	12.5	>100
7	$CH_2C_3H_5$ (cyclo-)	0.39	1.56	3.13	3.13	3.13	12.5	>100
8	$CH_2CH{=}CH_2$	0.2	0.39	1.56	0.78	0.39	6.25	100
9	$CH_2C{\equiv}CH$	0.39	0.2	1.56	0.39	0.39	12.5	>100
10	$CH_2C_6H_5$	0.2	6.25	6.25	6.25	1.56	25	>100
11	CH_2CH_2F	0.39	<0.1	0.39	<0.1	0.2	1.56	100
12	CH_2CH_2Cl	0.2	0.39	1.56	0.78	0.78	3.13	>100
13	CH_2CH_2OH	0.2	<0.1	0.39	0.2	0.2	3.13	>100
14	CH_2CH_2OMe	0.39	0.39	3.13	0.78	1.56	25	>100
15	CH_2CONH_2	0.78	<0.1	0.78	<0.1	0.2	25	>100
16	CMe_2CONH_2	0.78	3.13	3.13	3.13	0.78	6.25	50
17	CH_2CO_2Na	3.13	<0.1	6.25	<0.1	<0.1	3.13	>100
18	CMe_2CO_2Na	3.13	0.39	0.78	0.39	<0.1	1.56	12.5
19	$CHMeCO_2Na$	6.25	<0.1	1.56	<0.1	<0.1	3.13	>100
20	$CHEtCO_2Na$	6.25	0.2	1.56	0.2	<0.1	3.13	25
Ceftazidime		6.25	0.39	25	0.39	0.1	0.78	12.5
Cefmenoxime		1.56	0.2	6.25	0.39	<0.1	6.25	>100

[a] *S.a.*: *Staphylococcus aureus* 308 A-1, *E.c.*; *Escherichia coli* NIHJ JC-2, *E.cl.*: *Enterobacter cloacae* IFO 12937, *S.m.*: *Serratia marcescens* IFO 12648, *P.v.*: *Proteus vulgaris* IFO 3988, *P.a.*1: *Pseudomonas aeruginosa* IFO 3455, *P.a.*2: *P. aeruginosa* U-31.

The antibacterial activity of cephalosporins **17**～**20** with an R_1 of 1-carboxyalkyl groups against *S. aureus* markedly decreased and it was similar to that of CAZ, whereas the activity against both *P. vulgaris* and *P.a.* 1 increased. However, **18** with the same acyl group as CAZ showed more potent activity against *S. aureus* than did CAZ, and its activity against *P.a.* 1, *P.a.* 2 and *E. cloacae* was similar to that of CAZ.

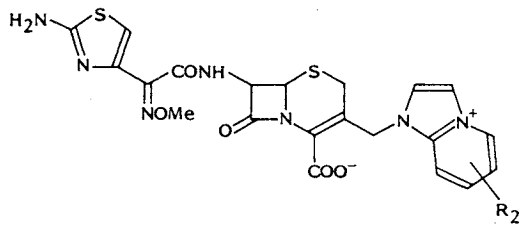
Table 2 shows the substituent effect of the imidazo[1,2-*a*]pyridinium ring of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]cephalosporins on the antibacterial activity.

The MICs of cephalosporins with an R_2 of methyl (**1**, **28**, **32**, **39**), halogeno (**31**, **35**～**37**, **41**), cyano (**27**, **38**), and benzyloxy (**40**) moieties were similar to that of **1**, but the antibacterial activity of those cephalosporins bearing hydrophilic R_2 groups, such as carbamoyl (**21**, **33**) and carboxyl (**22**, **34**) groups, against Gram-positive bacteria was decreased.

The cephalosporins with R_2 of halogeno, cyano, carbamoyl, and carboxy groups showed good activity against Gram-negative bacteria.

With reference to the effect of the substitution position in the imidazo[1,2-*a*]pyridine ring on the antibacterial activity, the cephalosporins having electron withdrawing groups, such as fluoro (**35**), chloro

Table 2. Antibacterial activity (MIC, μg/ml) of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(substituted imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylates (**1**, **21**～**41**).



Compound	R_2	*S.a.*	*E.c.*	*E.cl.*	*S.m.*	*P.v.*	*P.a.*1	*P.a.*2[a]
1	H	0.39	<0.1	0.39	0.2	0.2	6.25	>100
21	2-$CONH_2$	12.5	1.56	3.13	0.39	0.78	1.56	50
22	2-CO_2Na	6.25	0.39	3.13	1.56	0.2	12.5	50
23	2-CO_2Et	6.25	1.56	3.13	3.13	0.78	12.5	50
24	3-CH_2NMe_2	6.25	0.39	0.39	0.39	0.39	6.25	25
25	3-CH_2CN	0.78	<0.1	0.78	0.2	0.2	6.25	100
26	3-CH=NOH	3.13	<0.1	0.78	0.2	0.39	6.25	>100
27	3-CN	1.56	<0.1	1.56	0.2	0.2	1.56	50
28	5-Me	0.39	<0.1	0.78	0.39	0.2	12.5	>100
29	5-OMe	0.78	<0.1	0.78	0.39	0.39	25	>100
30	5-SMe	0.39	<0.1	0.78	0.2	0.2	12.5	>100
31	5-Cl	0.78	<0.1	1.56	0.39	0.2	3.13	>100
32	6-Me	0.78	<0.1	0.78	0.2	0.2	25	>100
33	6-$CONH_2$	0.78	<0.1	0.39	0.2	<0.1	3.13	>100
34	6-CO_2Na	3.13	<0.1	3.13	0.2	<0.1	12.5	>100
35	6-F	0.78	<0.1	0.39	<0.1	<0.1	3.13	>100
36	6-Cl	0.39	<0.1	0.78	0.2	0.2	6.25	>100
37	6-Br	0.78	<0.1	0.78	0.39	0.2	6.25	>100
38	6-CN	0.39	<0.1	0.39	0.2	0.2	1.56	100
39	8-Me	0.39	0.1	0.78	0.2	0.2	6.25	>100
40	8-$OCH_2C_6H_5$	0.39	3.13	3.13	3.13	3.13	6.25	100
41	8-F	0.39	<0.1	0.78	<0.1	<0.1	1.56	>100
Ceftazidime		6.25	0.39	25	0.39	0.1	0.78	12.5
Cefmenoxime		1.56	0.2	6.25	0.39	<0.1	6.25	>100

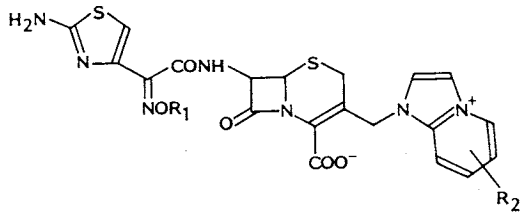
[a] Abbreviations: See footnote in Table 1.

(**36**) and cyano (**38**) at the 6 position in the imidazo[1,2-*a*]pyridine ring showed potent activity against both Gram-positive and Gram-negative bacteria including *P. aeruginosa*.

Furthermore, the effects of alkoxyimino groups of cephalosporins with 6-chloro (**42**～**44**), 6-cyano (**45**～**49**), 3-cyano (**50**, **51**), 6-carbamoyl (**52**), and 8-fluoroimidazo[1,2-*a*]pyridinium (**53**) moieties on the activity are shown in Table 3. These cephalosporins except **44**, **50** and **51** showed the same order of activity as **1**. It appeared that cephalosporins having an R_1 of an ethoxy group showed improved antibacterial activity against Gram-positive and Gram-negative bacteria including *P. aeruginosa*, and compound **49** showed the most potent activity against highly resistant *P. aeruginosa*.

In conclusion, we found that compound **45** has highly potent antibacterial activity against both Gram-positive and Gram-negative bacteria including *P. aeruginosa* and compound **49** shows activity superior to that of CAZ against Gram-negative bacteria including *P. aeruginosa*. These results imply that the delocalization of the imidazo[1,2-*a*]pyridinium cation leads to expanded antibacterial activity and that imidazo[1,2-*a*]pyridine is one of the useful moieties at the 3 position to improve the antibacterial activity

Table 3. Antibacterial activity (MIC, μg/ml) of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(substituted imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylates (**1**, **27**, **33**, **36**, **38**, **41**~**53**).



Compound	R_1	R_2	*S.a.*	*E.c.*	*E.cl.*	*S.m.*	*P.v.*	*P.a.*1	*P.a.*2[a]
1	Me	H	0.39	<0.1	0.39	0.2	0.2	6.25	>100
36	Me	6-Cl	0.39	<0.1	0.78	0.2	0.2	6.25	>100
42	Et	6-Cl	0.39	<0.1	0.78	0.2	0.2	3.13	50
43	CH_2CH_2F	6-Cl	0.39	<0.1	0.78	0.2	0.2	3.13	50
44	CMe_2CO_2Na	6-Cl	3.13	0.39	6.25	0.39	0.2	3.13	25
38	Me	6-CN	0.39	<0.1	0.39	0.2	0.2	1.56	100
45	Et	6-CN	0.39	0.2	0.78	0.39	0.39	1.56	25
46	*n*-Pr	6-CN	0.78	1.56	3.13	3.13	3.13	6.25	50
47	CH_2CH_2F	6-CN	0.78	<0.1	0.78	0.2	0.39	1.56	50
48	CH_2CH_2Cl	6-CN	0.78	0.78	3.13	1.56	1.56	3.13	50
49	CMe_2CO_2Na	6-CN	3.13	0.39	3.13	0.39	<0.1	1.56	6.25
27	Me	3-CN	1.56	<0.1	1.56	0.2	0.2	1.56	50
50	Et	3-CN	1.56	0.39	1.56	0.78	0.78	3.13	12.5
51	CMe_2CO_2Na	3-CN	12.5	0.78	1.56	0.78	0.39	6.25	12.5
33	Me	6-$CONH_2$	0.78	<0.1	0.39	0.2	<0.1	3.13	>100
52	Et	6-$CONH_2$	0.78	<0.1	1.56	0.39	0.78	3.13	>100
41	Me	8-F	0.39	<0.1	0.78	<0.1	<0.1	1.56	>100
53	Et	8-F	0.39	0.2	1.56	0.2	0.2	1.56	100
Ceftazidime			6.25	0.39	25	0.39	0.1	0.78	12.5
Cefmenoxime			1.56	0.2	6.25	0.39	<0.1	6.25	>100

[a] Abbreviations: See footnote in Table 1.

and expand the antibacterial spectrum of cephalosporins.

Experimental

MP's were determined on a Yanagimoto micro melting point apparatus and are uncorrected; boiling points are also uncorrected. IR spectra were taken on a Hitachi 215 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) or HA-100A (100 MHz) spectrometer using tetramethylsilane as the internal or external standard. Organic solvents were dried over anhydrous $MgSO_4$, and concentration by evaporation was carried out *in vacuo*. Column chromatography was carried out on Merck Kieselgel 60 (Art. No. 7734 or Art. No. 9385), Mitsubishi Chemical MCI gel CHP-20P, Rohm and Haas Amberlite XAD-2, and Pharmacia Fine Chemical Sephadex LH-20.

Determination of *In Vitro* Antibacterial Activity

The MICs against selected strains of Gram-positive and Gram-negative bacteria were determined by the standard serial 2-fold agar dilution method with Mueller-Hinton broth as the test medium, after incubation overnight at 37°C with an inoculum size of about 10^8 cfu/ml.

2-(2-Chloroacetamidothiazol-4-yl)-2(*Z*)-alkoxyiminoacetic Acid (**III**) (Method A)

2-(2-Chloroacetamidothiazol-4-yl)-2(*Z*)-methoxyiminoacetic acid (**IIIa**) and 2-(2-chloroacetamidothiazol-4-yl)-2(*Z*)-ethoxyiminoacetic acid (**IIIb**) were prepared according to the procedure of OCHIAI *et al.*[7].

2-(2-Chloroacetamidothiazol-4-yl)-2(*Z*)-carbamoylmethoxyiminoacetic Acid (**IIIo**) (Method A)

1) Ethyl 2-(2-Chloroacetamidothiazol-4-yl)-2(*Z*)-carbamoylmethoxyiminoacetate (**IIo**): Chloroacetyl chloride (2.2 g) was added dropwise to a solution of ethyl 2-(2-aminothiazol-4-yl)-2(*Z*)-carbamoylmethoxyiminoacetate (2.7 g) in DMF (10 ml) with ice-cooling and stirring. After stirring at room temperature for 3 hours, the reaction mixture was poured into ice water (100 ml). The crystalline precipitate was collected by filtration and dried to give 3.18 g (95%) of **IIo**: MP 187~189°C.

2) 2-(2-Chloroacetamidothiazol-4-yl)-2(*Z*)-carbamoylmethoxyiminoacetic Acid (**IIIo**): A suspension of **IIo** (3.18 g) in 1 N NaOH (30 ml) was stirred at room temperature for 1 hour. After neutralization with conc HCl, the crystalline precipitate was collected by filtration, washed with water and dried to give 2.0 g (66%) of **IIIo**: MP 192~193°C; ^{1}H NMR (DMSO-d_6) δ 4.57 (2H, s), 4.72 (2H, s), 7.12 and 7.57 (2H, br), 7.77 (1H, s).

General Preparation of 2-(2-Aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetic Acid (**VIIIb~VIIIp**) (Method B)

1) Ethyl 2-(2-Aminothiazol-4-yl)-2(*Z*)-benzyloxyiminoacetate (**VIIj**): A mixture of ethyl 2-(2-aminothiazol-4-yl)-2(*Z*)-hydroxyiminoacetate (**VI**, 10 g), benzyl bromide (20 g) and anhydrous K_2CO_3 (10 g) in Me_2CO (250 ml) was refluxed for 3 hours with stirring. After cooling, the solid was filtered off and the filtrate was evaporated. The residue was recrystallized from diisopropyl ether to give 10 g (71%) of **VIIj**: MP 137~138°C.

2) 2-(2-Aminothiazol-4-yl)-2(*Z*)-benzyloxyiminoacetic Acid (**VIIIj**): A mixture of **VIIj** (9.0 g) and 50% aq NaOH (4.8 ml) in a mixture of THF (20 ml) and MeOH (20 ml) was stirred at room temperature for 4 hours. The mixture was evaporated and the residue was diluted with H_2O. The solution was neutralized with conc HCl and then extracted with EtOAc (200 ml). The extract was washed with satd aq NaCl, dried and evaporated to give 6.0 g (73%) of **VIIIj**: MP 140~145°C; ^{1}H NMR (DMSO-d_6) δ 5.13 (2H, s), 6.83 (1H, s), 7.20 (2H, br), 7.33 (5H, s).

Ethyl 2-(2-Aminothiazol-4-yl)-2(*Z*)-(2-fluoroethoxyimino)acetate (**VIIk**)

A mixture of **VI** (10.5 g), 2-fluoroethyl bromide (10 g) and anhydrous K_2CO_3 (11.3 g) in DMSO (100 ml) was kept at 60°C for 1 hour with stirring. The reaction mixture was poured into a mixture of EtOAc (200 ml) and H_2O (200 ml). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with satd aq NaCl, dried and evaporated to give 8.3 g (65%) of **VIIk**: MP 98~100°C; ^{1}H NMR (DMSO-d_6) δ 1.25 (3H, t, J=6 Hz), 4.29 (2H, q, J=6 Hz), 4.0~5.0 (4H, m), 6.91 (1H, s), 7.23 (2H, br).

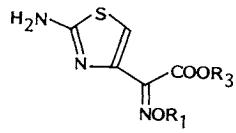
2-(2-Aminothiazol-4-yl)-2(*Z*)-(1-*tert*-butoxycarbonylethoxyimino)acetic Acid (**XIc**) (Method C)

XI was prepared according to the procedure of TAKANOHASHI *et al.*[8].

1) 2-Methylthioethyl 2-(2-Aminothiazol-4-yl)-2(*Z*)-(1-*tert*-butoxycarbonylethoxyimino)acetate (**Xc**): A mixture of 2-methylthioethyl 2-(2-aminothiazol-4-yl)-2(*Z*)-hydroxyiminoacetate (**IX**, 10 g). *tert*-Butyl 2-bromobutyrate (10 g) and anhydrous K_2CO_3 (7 g) in Me_2CO (250 ml) was stirring at 60~70°C for 16 hours. After cooling, the solid was filtered off and the filtrate was evaporated. The residue was dissolved in EtOAc (100 ml), and the solution was washed with satd aq NaCl, dried and then evaporated to give 12.6 g (83%) of **Xc**: ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, t, J=7 Hz), 1.48 (9H, s), 1.65~2.15 (2H, m), 2.18 (3H, s), 2.82 (2H, t, J=7 Hz), 4.10~4.65 (3H, m), 6.25 (2H, br), 6.27 (1H, s).

2) **XIc**: H_2O_2 (30% aq soln, 10 ml) was added dropwise to a solution of **Xc** (10 g) and ammonium molybdate (0.1 g) in 80% aq Me_2CO (125 ml). After stirring at room temperature for 16 hours, the mixture was neutralized with aq sodium sulfite solution and then extracted with EtOAc to give a solution containing methylsulfonylethyl 2-(2-aminothiazol-4-yl)-2(*Z*)-(1-*tert*-butoxycarbonylethoxyimino)acetate. This solution was diluted with 50% aq Me_2CO (340 ml), adjusted to pH 11 with 30% aq K_2CO_3, and the mixture was stirred at 30~40°C for 2 hours. The mixture was neutralized with 1 N HCl and the organic layer was discarded. The aqueous layer was acidified with 1 N HCl and extracted with methyl ethyl ketone (500 ml). The combined extract was washed with satd aq NaCl, dried and evaporated to give 3.2 g (40%) of **XIc**: MP 121~124°C.

Table 4. 2-(2-Aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetic acid derivatives (**VII**, **VIII**, **X**, **XI**).



VII R_3=Et
VIII R_3=H
X R_3=CH_2CH_2SMe
XI R_3=H

Compound No.	R_1	Ester (**VII**, **X**)			Acid (**VIII**, **XI**)		
		Method	Yield (%)	MP (°C)	Yield (%)	^{1}H NMR (DMSO-d_6) δ thiazole	
						5-H (s)	NH_2(br s)
			VII:			**VIII**:	
b	Et[a]	B	80		90	6.83	7.24
c	*n*-Pr[a]	B	72	144~146	59	6.83	7.20
d	*n*-Bu	B	28	125.5~127	68	6.82	7.20
e	C_6H_{13}[a]	B	40	75~76	67	6.80	7.27
f	C_5H_9 (cyclo-)	B	49		66	6.84	7.17
g	$CH_2C_3H_5$ (cyclo-)	B	36	110~113	59	6.83	7.21
h	$CH_2CH=CH_2$	B	78		69	6.82	7.20
i	$CH_2C\equiv CH$	B	65		70	6.85	7.19
j	$CH_2C_6H_5$	B	71	137~138	73	6.83	7.20
k	CH_2CH_2F	B	65	98~100	92	6.69	7.20
l	CH_2CH_2Cl	B	41		78	6.84	7.23
m	CH_2CH_2OH	B	36		56	6.82	7.30
n	CH_2CH_2OMe	B	38		77	6.79	7.16
o	CH_2CONH_2	B	87	185~187	72	6.80	7.20
p	CMe_2CONH_2	B	42		58	6.81	7.20
			X:			**XI**:	
a	$CH_2CO_2CMe_3$[8]	C	92		79	6.81	7.20
b	$CMe_2CO_2CMe_3$[8]	C	55		87	6.78	7.19
c	$CHMeCO_2CMe_3$[8]	C	94	83~84	68	6.81	7.20
d	$CHEtCO_2CMe_3$	C	83		40	6.82	7.22

[a] TAKATANI, T.; Y. TAKASUGI, S. MASUGI, T. CHIBA, H. KOUCHI, T. TAKANO & H. NAKANO: Nippon Kagakukaishi 1981: 785~804, 1981.

Anal Calcd for $C_{13}H_{19}N_3O_5S\cdot 2H_2O$: C 42.73, H 6.34, N 11.49.
Found: C 42.37, H 6.02, N 11.40.

The other 2-(2-aminothiazol-4-yl)-2(*Z*)-(substituted)alkoxyiminoacetic acids (**VIII** and **XI**) were prepared according to the above mentioned procedure. When the ester (**VII**) was not obtained in crystalline form, **VII** was hydrolyzed to the corresponding acid, and the structure was determined by ^{1}H NMR.

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**Va**)

1) 7β-[2-(2-Chloroacetamidothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**IVa**): A solution of **IIIa** (69.3 g) in CH_2Cl_2 (1 liter) was stirred with PCl_5 (50.5 g) at -10°C for 15 minutes. *n*-Hexane (500 ml) was added to the reaction mixture and the resulting mixture was stirred for 15 minutes. The crystalline precipitate was collected by filtration, washed with a mixture (500 ml) of CH_2Cl_2 and *n*-hexane (2 : 1) and dried to give 2-(2-chloroacetamidothiazol-4-yl)-2(*Z*)-methoxyiminoacetyl chloride hydrochloride[7]. The entire amount of 2-(2-chloroacetamidothiazol-4-yl)-2(*Z*)-methoxyiminoacetyl chloride hydrochloride was added portionwise to an aqueous solution of

7β-amino-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (7-AACA, 62.8 g) and $NaHCO_3$ (109 g) in H_2O (500 ml) and the mixture was stirred for 20 minutes. The reaction mixture was adjusted to pH 3.0 with conc HCl and saturated with NaCl. The organic layer was separated and the aqueous layer was extracted with THF (500 ml). The combined organic layer was dried and evaporated. The residue was crystallized from EtOAc to give 100 g (87%) of **IVa**: IR (KBr) cm^{-1} 1780, 1740, 1700, 1655, 1540; ^1H NMR (DMSO-d_6) δ 2.20 (3H, s), 3.45 and 3.68 (2H, ABq, $J=18$ Hz), 3.65 (2H, s), 3.92 (3H, s), 4.38 (2H, s), 4.79 and 5.09 (2H, ABq, $J=13$ Hz), 5.18 (1H, d, $J=5$ Hz), 5.85 (1H, dd, $J=5$ and 8 Hz), 7.44 (1H, s), 9.66 (1H, d, $J=8$ Hz), 12.85 (1H, br).

Anal Calcd for $C_{20}H_{20}ClN_5O_9S_2$: C 41.85, H 3.51, N 12.20.
Found: C 41.52, H 3.55, N 11.96.

2) **Va**: A mixture of **IVa** (100 g), $NaHCO_3$ (14.6 g) and sodium *N*-methyldithiocarbamate (45 g) in H_2O (500 ml) was stirred with EtOAc (500 ml) at 25°C for 2 hours. The organic layer was discarded and the aqueous layer was washed with EtOAc. The aqueous layer was adjusted to pH 3 with conc HCl and the precipitate was collected by filtration and dried to give 61 g (59%) of **Va**.

Anal Calcd for $C_{18}H_{19}N_5O_8S_2 \cdot H_2O$: C 41.94, H 4.11, N 13.60.
Found: C 42.19, H 4.30, N 13.55.

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-ethoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**Vb**)

Vb was prepared from **IVb** and 7-AACA according to the procedure described for **Va**. Yield and ^1H NMR data are shown in Table 5.

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-carbamoylmethoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**Vo**)

1) 7β-[2-(2-Chloroacetamidothiazol-4-yl)-2(*Z*)-carbamoylmethoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**IVo**): 1-Hydroxybenzotriazole (HOBT, 11.4 g) and *N*,*N*-dicyclohexylcarbodiimide (DCC, 22 g) were added to a solution of **IIIo** (24 g) in DMF (100 ml), and the reaction mixture was stirred at room temperature for 2 hours. The solid was filtered off, and the filtrate was added to a solution of 7-AACA (22 g) and triethylamine (21 ml) in DMF (70 ml) at 0°C. After stirring at 20°C for 1 hour, a mixture of methyl ethyl ketone (60 ml) and satd aq NaCl (1 liter) were added to the reaction mixture and the mixture was again stirred. The organic layer was separated, dried and evaporated. EtOAc was added to the residue, and the precipitate was collected by filtration and dried to yield 19 g (44%) of **IVo**.

2) Sodium *N*-methyl dithiocarbamate (20 g) and EtOAc (150 ml) were added to a solution of **IVo** (19 g) in H_2O (150 ml), and the mixture was stirred at room temperature for 8 hours. The reaction mixture was adjusted to pH 4 with AcOH, the aqueous layer was separated, evaporated, and the residual solution was lyophilized. The powder obtained was dissolved in H_2O (100 ml) and extracted with methyl ethyl ketone (100 ml). The extract was dried, and evaporated to afford 6.0 g (36%) of **Vo** as powder. ^1H NMR data are presented in Table 5.

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-ethoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**Vb**)

HOBT (15 g) and DCC (20.6 g) were added to a solution of 2-(2-aminothiazol-4-yl)-2(*Z*)-ethoxyiminoacetic acid (**VIIIb**, 23 g) in DMF (100 ml), and the mixture was stirred at room temperature for 1.5 hours. The solid was filtered off, and the filtrate was added to a solution of 7-AACA (31 g) and triethylamine (28 ml) in DMF (100 ml) with ice-cooling and stirring. After stirring at room temperature for 3 hours, the reaction mixture was diluted with Et_2O (500 ml) and the precipitate was collected by filtration. The solid was dissolved in H_2O (100 ml) and the solution was adjusted to pH 3.0 with 10% HCl and then extracted with methyl ethyl ketone (400 ml). The extract was washed with H_2O, dried and evaporated. The residue was washed with EtOAc to give 31 g (65%) of **Vb** as powder. IR and ^1H NMR data are listed in Table 5.

Table 5. IR and ^{1}H NMR data for 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylates (**V**, **XII**).

Compound No.	Method	Yield (%)	IR (KBr) cm^{-1}	^{1}H NMR (δ, (J=Hz), DMSO-d_6)									
				Cephem nuclei				CONH d (8)	3-OAcAc		7-Acyl		R_1
				2-CH_2 ABq (18)	3-CH_2 ABq (14)	6-H d (5)	7-H dd (5, 8)		CH_3 (s)	CH_2 (s)	5-H (s)	NH_2 (br)	
Va	A	68	1770, 1710	3.43, 3.65	4.78, 5.06	5.14	5.79	9.56	2.20	3.63	6.73	7.17	3.86 (s)
b	A	93	1780, 1720	3.45, 3.70	4.70, 5.08	5.25	5.90	9.80	2.25	3.63	6.90	7.20	1.30 (t, 7), 4.20 (q, 7)
	B	62											
c	B	48	1790, 1750	3.45, 3.70	4.76, 5.08	5.04	5.80	9.70	2.18	3.64	6.87	7.13	0.90 (t, 7), 1.45~1.85 (m), 4.10 (t, 7)
d	B	70	1780, 1750	3.44, 3.65	4.81, 5.08	5.14	5.78	9.48	2.22	3.63	6.69	7.12	0.92 (t, 7), 1.1~1.8 (m), 4.08 (t, 7)
e	B	46	1780, 1750	3.38, 3.61	4.77, 5.05	5.10	5.74	9.48	2.20	3.63	6.70	7.14	0.87 (t), 1.28 (br s), 2.20 (s), 4.06 (t, 7)
f	B	51	1780, 1750	3.45, 3.66	4.81, 5.15	5.10	5.78	9.46	2.20	3.64	6.70	7.20	1.4~2.0 (m)
g	B	90	1760, 1735	3.42, 3.66	4.80, 5.08	5.15	5.78	9.52	2.20	3.64	6.70	7.22	0.1~0.6 (m), 0.7~1.5 (m), 3.91 (d, 7)
h	B	83	1780, 1720	3.45, 3.66	4.80, 5.10	5.26	5.90	9.83	2.30	—	6.80	7.20	4.64 (d, 6), 5.23 (d, 6), 5.90~6.20 (m)
i	B	45	1780, 1720	3.45, 3.65	4.80, 5.10	5.25	5.90	9.83	2.20	3.64	6.81	7.19	3.40 (t, 3), 4.71 (d, 3)

j	B	71	1770, 1730	3.2～3.8 (m)	4.82, 5.12	5.10	5.84	9.65	2.21	—	6.80	7.22	5.18 (s), 7.38 (s)
k	A B	57 52	1770, 1740	3.50～3.7 (m)	4.80, 5.03	5.20	5.86	9.70	2.20	3.66	6.90	7.13	4.10～4.66 (m)
l	B	66	1770, 1705	3.05, 3.50	4.76, 5.06	5.16	5.80	9.60	2.20	3.60	6.76	7.20	3.73～3.90 (m), 4.20～4.5 (m)
m	B	51	1780, 1750	3.4～3.7 (m)	4.95, 5.12	5.04	5.75	9.46	2.20	3.65	6.70	7.20	4.32 (t, 6), 2.9～3.2 (m)
n	B	57	1770, 1750	3.4～3.7 (m)	4.81, 5.08	—	5.77	9.51	2.20	—	6.73	7.13	3.28 (s), 4.19 (t, 7), 3.2～3.4 (m)
o	A	16	1780, 1720	3.40, 3.65	4.80, 5.06	5.16	5.80	9.60	2.10	3.63	6.74	—	4.40 (s), 7.05～7.40 (m)
p	B	62	1780, 1720	3.11, 3.72	4.80, 5.12	4.92	5.60	9.38	2.25	3.60	6.70	7.20	1.39 (s), 1.42 (s), 6.7～7.1 (m)
XIIa	C	65	1790, 1730	3.40, 3.60	4.81, 5.10	5.20	5.80	9.30	2.20	—	6.70	—	1.50 (s), 4.40 (s)
b	C	50	1780, 1720	3.4～3.7 (m)	4.70, 5.10	5.19	5.82	9.29	2.20	—	6.73	7.19	1.42 (s), 3.4～3.7 (m)
c	C	45	1780, 1720	3.44, 3.68	4.80, 5.11	5.18	5.84	9.40	2.20	3.64	6.77	7.18	0.88, 0.95 (t, 7), 4.5～4.7 (m)
d	C	54	1780, 1730	3.22, 3.51	4.77, 5.12	5.16	5.85	9.46	2.20	—	6.77	—	0.90, 0.93 (d, 7), 1.42 (s), 1.5～1.9 (m), 4.3～4.6 (m)

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(1-*tert*-butoxycarbonylethoxyimino)acetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic Acid (**XIIc**)

HOBT (1.5 g) and DCC (2.1 g) were added to a solution of 2-(2-aminothiazol-4-yl)-2(*Z*)-(1-*tert*-butoxycarbonylethoxyimino)acetic acid (**XIc**, 3 g) in DMF (20 ml), and the mixture was stirred at room temperature for 1 hour. The solid was filtered off, and the filtrate was added to a solution of 7-AACA (3.1 g) and triethylamine (2 g) in DMF (20 ml). The reaction mixture was then stirred at room temperature for 6 hours. The solid was filtered off and the filtrate was diluted with Et_2O (500 ml). After decanting off the Et_2O, the residual solid was dissolved in H_2O (10 ml). The aqueous solution was adjusted to pH 3.0 with 1 N HCl and extracted with methyl ethyl ketone (200 ml). The extract was washed with H_2O, dried and evaporated. The residue was solidified with *n*-hexane to give 3.9 g (45%) of **XIIc**. IR and ^1H NMR spectra are shown in Table 5.

The other 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(3-oxobutyryloxymethyl)-3-cephem-4-carboxylic acid (**V** and **XII**) were prepared by a procedure similar to that mentioned above and the relevant IR and ^1H NMR data are shown in Table 5.

Preparation of Imidazo[1,2-*a*]pyridine Derivatives (**XIII**)

The known imidazo[1,2-*a*]pyridines (**XIII**) were prepared following the procedures in the literatures[9~17].

Imidazo[1,2-*a*]pyridine (**XIIIa**): BP 95~105°C/0.1 mmHg (literature[9] BP 103°C/0.1 mmHg), 2-carbamoylimidazo[1,2-*a*]pyridine (**XIIIb**): MP 218~220°C (literature[10] MP 229~230°C), 2-carboxyimidazo[1,2-*a*]pyridine (**XIIIc**): MP >300°C (literature[10] MP 232~234°C), 2-ethoxycarbonylimidazo[1,2-*a*]pyridine (**XIIId**): MP 55~56°C (literature[10] MP 57~59°C), 3-dimethylaminomethylimidazo[1,2-*a*]pyridine (**XIIIe**): MP 81~82°C (literature[9] MP 77.5~80.5°C), 3-cyanomethylimidazo[1,2-*a*]pyridine (**XIIIf**): MP 143~145°C (literature[11] MP 145~146°C), 3-hydroxyiminomethylimidazo[1,2-*a*]pyridine (**XIIIg**): MP 206~207°C (dec) (literature[12] MP 206~207°C), 3-cyanoimidazo[1,2-*a*]pyridine (**XIIIh**): MP 143~145°C (literature[11] MP 156~157°C), 5-methylimidazo[1,2-*a*]pyridine (**XIIIi**): Oil (literature[13] BP 104~105°C/0.05 mmHg), 5-methoxyimidazo[1,2-*a*]pyridine (**XIIIj**): MP 160~162°C (literature[14] MP 161~162°C), 5-chloroimidazo[1,2-*a*]pyridine (**XIIIl**): BP 93~95°C/0.1 mmHg, 6-methylimidazo[1,2-*a*]pyridine (**XIIIm**): Semi solid (literature[15] hydrochloride MP 142.5~149°C), 6-chloroimidazo[1,2-*a*]pyridine (**XIIIq**): MP 64~65°C (literature[16] BP 132°C/1.5 mmHg), 6-bromoimidazo[1,2-*a*]pyridine (**XIIIr**): MP 54~55°C (literature[16] MP 53~55°C), 8-methylimidazo[1,2-*a*]pyridine (**XIIIt**): Oil[15], 8-benzyloxyimidazo[1,2-*a*]pyridine (**XIIIu**): MP 97~98°C (literature[17] MP 105~106°C), and 3-formylimidazo[1,2-*a*]pyridine (**XIIIw**): MP 123~124°C (literature[12] MP 127~129°C).

5-Methylthioimidazo[1,2-*a*]pyridine (**XIIIk**)

A mixture of **XIIIl** (5.0 g) and MeSNa (5.0 g) in DMF (100 ml) was stirred at room temperature for 1 hour. After evaporating the solvent, the residue was dissolved in CH_2Cl_2 (200 ml). The organic solution was washed with H_2O, dried and evaporated. The residue was purified by column chromatography on silica gel to give 3 g (56%) of **XIIIk** as an oil: ^1H NMR ($CDCl_3$) δ 2.55 (3H, s), 6.63 (1H, d, J=7 Hz), 7.07 (1H, dd, J=7 and 9 Hz), 7.43 (1H, d, J=9 Hz), 7.61 (2H, s).

6-Carbamoylimidazo[1,2-*a*]pyridine (**XIIIn**)

A mixture of 6-aminonicotinamide (10 g), 40% aq chloroacetaldehyde (11 g) and $NaHCO_3$ (12.5 g) in EtOH (100 ml) was refluxed for 4 hours. After removing EtOH by evaporation, the residue was dissolved in H_2O (100 ml). The solution was adjusted to pH 10.0 with 10% NaOH and extracted with a mixture of THF - EtOAc (1 : 1, 200 ml). The extract was dried and evaporated, and the residue was recrystallized from a mixture of MeOH and Et_2O (1 : 1) to give 3.5 g (30%) of **XIIIn** as colorless needles: MP 202~204°C; ^1H NMR (DMSO-d_6) δ 7.65 (3H, s), 8.03 (1H, s), 9.10 (1H, s).

Anal Calcd for $C_8H_7N_3O$: C 59.62, H 4.38, N 26.09.
Found: C 59.39, H 4.61, N 25.79.

6-Cyanoimidazo[1,2-*a*]pyridine (**XIIIs**)

A mixture of **XIIIn** (2.6 g) in $POCl_3$ (30 ml) was refluxed for 16 hours. After evaporating the $POCl_3$,

the residue was poured into crushed ice. After neutralizing with Na_2CO_3, the solution was extracted with EtOAc. The extract was washed with H_2O, dried and evaporated to give 2 g (87%) of **XIIIs** as colorless needles: MP 166~167°C.

Anal Calcd for $C_8H_5N_3$: C 67.13, H 3.52, N 29.35.
Found: C 67.37, H 3.62, N 28.99.

6-Carboxyimidazo[1,2-*a*]pyridine (**XIIIo**)

XIIIn (10 g) and NaOH (8.4 g) in 80% aq EtOH (130 ml) was refluxed for 1.5 hours. After cooling, the solid was filtered off. The filtrate was concentrated, and the residual aqueous soln was adjusted to pH 3.0 with conc HCl. The crystalline precipitate was collected by filtration and dried to give 10.7 g (94%) of **XIIIo**; MP >300°C.

8-Fluoroimidazo[1,2-*a*]pyridine (**XIIIv**)

A mixture of bromoacetaldehyde diethylacetal (74 g) in 47% HBr (18.5 ml) and H_2O (18.5 ml) was heated at 100°C for 1 hour with stirring. After cooling, the mixture was diluted with EtOH (100 ml), and $NaHCO_3$ was added to the solution until the evolution of carbon dioxide ceased. The solid was filtered off, and the filtrate was refluxed with 2-amino-3-fluoropyridine (21.1 g) and $NaHCO_3$ (17.8 g) for 5 hours. After evaporating the solvent, H_2O (100 ml) was added to the residue. The mixture was extracted with $CHCl_3$ (300 ml). The extract was dried and evaporated, and the residue was distilled under reduced pressure to give 12 g (52%) of **XIIIv**; BP 91~100°C/1~1.5 mmHg: ^1H NMR ($CDCl_3$) δ 6.53~7.33 (2H, m), 7.60~7.70 (2H, m), 7.88~8.03 (1H, m).

6-Fluoroimidazo[1,2-*a*]pyridine (**XIIIp**) was prepared from 2-amino-5-fluoropyridine according to the procedure mentioned above: Oil; ^1H NMR ($CDCl_3$) δ 6.6~7.4 (2H, m), 7.5~7.7 (2H, m), 7.9~8.1 (1H, m).

General Method of the Preparation of 3-Azoliummethyl Cephalosporins

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)-methyl-3-cephem-4-carboxylate (**1**) (Method D)

A mixture of **Va** (4 g), **XIIIa** (4 g) and KI (4 g) in 50% aq MeCN (40 ml) was kept at 70°C for 2 hours with stirring. After evaporating the solvent, MeCN (100 ml) was added to the residue and the resulting precipitate was collected by filtration. The powder was dissolved in a small amount of H_2O and chromatographed on silica gel successively with MeCN and 80% aq MeCN as eluents. The fractions containing the desired compound were combined, concentrated and then lyophilized. The powder obtained was dissolved in H_2O (5 ml) and chromatographed on Amberlite XAD-2 with 10% aq EtOH as the eluent. The fractions containing the cephalosporin derivative were combined, evaporated and then lyophilized to give 1 g (9%) of **1**. Analytical results are shown in Tables 6~10.

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-carboxymethoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate Monosodium Salt (**17**) (Method E)

A mixture of **XIIa** (3 g), **XIIIa** (3 g) and KI (3 g) in 50% aq MeCN (60 ml) was kept at 70°C for 2 hours with stirring. The reaction mixture was evaporated and H_2O (10 ml) was added to the residue which was then washed with EtOAc (2×20 ml). The aqueous layer was chromatographed on Amberlite XAD-2 with 20% aq EtOH as the eluent. The fractions containing the desired crude compound were combined, evaporated and then lyophilized to afford crude 0.9 g of 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-*tert*-butoxycarbonylmethoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylate (**XIV17**) as powder. **XIV17** was stirred with TFA at room temperature for 2 hours. After evaporating the solvent, the residue was dissolved in 5% aq $NaHCO_3$ (5 ml) and chromatographed on Amberlite XAD-2 with H_2O as the eluent. The fractions containing the desired compound were combined and concentrated. The residue was lyophilized to give 0.4 g (11%) of **17**. Analytical results are shown in Tables 6~10.

The other azoliummethyl cephalosporins were prepared from **Va~Vp**, **XIIa~XIId** and imidazo[1,2-*a*]pyridine derivatives (**XIII**) according to Method D or Method E similar to that described above. Their structures and analytical results are shown in Tables 6~10.

Table 6. IR and analytical data for 7β-[2-(2-aminothiazol-4-yl)-2(Z)-alkoxyiminoacetamido]-3-(imidazo[1,2-a]pyridinium-1-yl)methyl-3-cephem-4-carboxylates (**1**~**20**).

Compound No.	Method	Yield (%)	Formula	Elemental analysis (%)						IR (KBr) cm^{-1}
				Calcd			Found			
				C	H	N	C	H	N	
1	D	9	$C_{21}H_{19}N_7O_5S_2 \cdot 3.5H_2O$	43.74	4.55	17.00	44.00	4.29	17.23	1765, 1670, 1605
2	D	5	$C_{22}H_{21}N_7O_5S_2 \cdot 3H_2O$	45.43	4.68	16.86	45.64	4.26	16.78	1770, 1610, 1530
3	D	3	$C_{23}H_{23}N_7O_5S_2 \cdot 4H_2O$	45.02	5.09	15.98	44.95	4.66	15.80	1775, 1650, 1610
4	D	10	$C_{24}H_{25}N_7O_5S_2 \cdot 3.5H_2O$	46.59	5.21	15.85	46.87	5.10	15.65	1770, 1670, 1610
5	D	5	$C_{26}H_{29}N_7O_5S_2 \cdot 2.5H_2O$	49.67	5.45	15.60	49.53	5.53	15.23	1770, 1670, 1610
6	D	5	$C_{25}H_{25}N_7O_5S_2 \cdot 4H_2O$	46.94	5.20	15.33	46.82	5.36	15.12	1770, 1665, 1610
7	D	19	$C_{24}H_{23}N_7O_5S_2 \cdot 6.5H_2O$	42.98	5.41	14.62	43.09	5.60	14.74	1770, 1620, 1530
8	D	22	$C_{23}H_{21}N_7O_5S_2 \cdot 3H_2O$	46.54	4.58	16.52	46.70	4.41	16.75	1770, 1670, 1610
9	D	8	$C_{23}H_{19}N_7O_5S_2 \cdot 3.5H_2O$	45.99	4.36	16.32	46.07	4.51	16.18	1770, 1665, 1610
10	D	7	$C_{27}H_{23}N_7O_5S_2 \cdot 3.5H_2O$	49.69	4.63	15.02	49.77	4.38	14.92	1765, 1680, 1640
11	D	3	$C_{22}H_{20}FN_7O_5S_2 \cdot 4H_2O$	42.78	4.57	15.87	42.57	4.27	15.71	1760, 1610, 1525
12	D	4	$C_{22}H_{20}ClN_7O_5S_2 \cdot 2.5H_2O$	43.53	4.15	16.15	43.25	4.03	15.94	1760, 1605, 1520
13	D	5	$C_{22}H_{21}N_7O_6S_2 \cdot 4H_2O$	42.92	4.75	15.93	42.86	4.54	15.70	1770, 1650, 1610
14	D	7	$C_{23}H_{23}N_7O_6S_2 \cdot 3.5H_2O$	44.51	4.87	15.80	44.67	4.75	15.25	1775, 1670, 1610
15	D	2	$C_{22}H_{20}N_8O_6S_2 \cdot 5.5H_2O$	40.86	4.68	17.33	40.54	4.15	17.09	1770, 1675, 1610
16	D	2	$C_{24}H_{24}N_8O_6S_2 \cdot 4H_2O$	43.90	4.91	17.06	43.94	5.03	16.90	1780, 1725, 1670
17	E	11	$C_{22}H_{18}N_7NaO_7S_2 \cdot 4H_2O$	40.55	4.02	15.05	40.39	3.75	15.22	1770, 1660, 1605
18	E	14	$C_{24}H_{22}N_7NaO_7S_2 \cdot 3H_2O$	43.57	4.27	14.82	43.67	4.39	14.60	1765, 1670, 1600
19	E	4	$C_{23}H_{20}N_7NaO_7S_2 \cdot 6H_2O$	39.37	4.60	13.97	39.65	4.20	13.30	1780, 1670, 1610
20	E	2	$C_{24}H_{22}N_7NaO_7S_2 \cdot 4.5H_2O$	41.86	4.54	14.24	41.67	4.38	14.58	1780, 1670, 1600

Table 7. IR and analytical data for 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylates (**21**~**53**).

Compound No.	Method	Yield (%)	Formula	Elemental analysis (%)						IR (KBr) cm^{-1}
				Calcd			Found			
				C	H	N	C	H	N	
21	D	1	$C_{22}H_{20}N_8O_6S_2 \cdot 8.5H_2O$	37.23	5.26	15.79	37.37	5.43	15.29	1765, 1750, 1690
22	D	5	$C_{22}H_{18}N_7NaO_7S_2 \cdot 4H_2O$	40.55	4.02	15.05	40.59	3.71	14.57	1765, 1620, 1520
23	D	4	$C_{24}H_{23}N_7O_7S_2 \cdot 5H_2O$	42.66	4.92	14.51	42.51	4.56	14.57	1770, 1670, 1600
24	D	5	$C_{24}H_{26}N_8O_5S_2 \cdot 4H_2O$	44.85	5.33	17.44	44.59	5.06	17.20	1770, 1660, 1610
25	D	5	$C_{23}H_{20}N_8O_5S_2 \cdot 4H_2O$	44.23	4.52	17.94	44.16	4.63	17.93	2260, 1765, 1650
26	D	10	$C_{22}H_{20}N_8O_6S_3 \cdot 4H_2O$	42.03	4.49	17.83	41.99	4.70	17.54	1770, 1690, 1670
27	D	5	$C_{22}H_{18}N_8O_5S_2 \cdot 4H_2O$	43.27	4.29	18.35	43.63	4.29	18.16	2245, 1770, 1660
28	D	18	$C_{22}H_{21}N_7O_5S_2 \cdot 4.5H_2O$	43.42	4.97	16.11	43.06	4.73	16.13	1770, 1680, 1605
29	D	11	$C_{22}H_{21}N_7O_6S_2 \cdot 3.5H_2O$	43.56	4.65	16.16	43.63	4.57	16.22	1765, 1650, 1620
30	D	12	$C_{22}H_{21}N_7O_5S_3 \cdot 4H_2O$	41.83	4.63	15.52	41.91	4.40	15.20	1770, 1660, 1620
31	D	12	$C_{21}H_{18}ClN_7O_5S_2 \cdot 4H_2O$	40.68	4.23	15.81	40.78	3.93	15.91	1770, 1670, 1610
32	D	19	$C_{22}H_{21}N_7O_5S_2 \cdot 5.5H_2O$	42.17	5.15	15.65	41.86	4.21	15.46	1765, 1610, 1535
33	D	10	$C_{22}H_{20}N_8O_6S_2 \cdot 4.5H_2O$	41.44	4.58	17.57	41.65	4.36	17.66	1770, 1680, 1620
34	D	4	$C_{22}H_{18}N_7NaO_7S_2 \cdot 5H_2O$	39.46	4.21	14.64	39.39	4.11	14.53	1765, 1665, 1610
35	D	3	$C_{21}H_{18}FN_7O_5S_2 \cdot 4H_2O$	41.79	4.34	16.24	41.55	4.02	15.88	1765, 1660, 1610
36	D	15	$C_{21}H_{18}ClN_7O_5S_2 \cdot 4H_2O$	40.68	4.23	15.81	40.63	3.96	15.92	1765, 1660, 1610
37	D	9	$C_{21}H_{18}BrN_7O_5S_2 \cdot 2H_2O$	40.13	3.53	15.60	40.30	3.74	15.29	1765, 1670, 1610
38	D	10	$C_{22}H_{18}N_8O_5S_2 \cdot 5H_2O$	42.03	4.49	17.83	42.28	4.12	17.65	2250, 1770, 1670
39	D	8	$C_{22}H_{21}N_7O_5S_2 \cdot 3.5H_2O$	44.74	4.78	16.60	44.48	4.43	16.85	1780, 1665, 1615
40	D	3	$C_{28}H_{25}N_7O_6S_2 \cdot 4.5H_2O$	47.99	4.89	13.99	47.89	4.60	13.99	1770, 1670, 1610
41	D	10	$C_{21}H_{18}FN_7O_5S_2 \cdot 4H_2O$	41.79	4.34	16.24	41.55	4.11	15.88	1770, 1660, 1615
42	D	11	$C_{22}H_{20}ClN_7O_5S_2 \cdot 4H_2O$	41.67	4.45	15.46	41.85	4.09	15.69	1760, 1660, 1615
43	D	3	$C_{22}H_{19}ClFN_7O_5S_2 \cdot 3H_2O$	41.67	3.97	15.46	41.49	4.26	15.31	1765, 1670, 1610
44	E	5	$C_{24}H_{21}ClN_7NaO_7S_2 \cdot 4H_2O$	40.37	4.09	13.73	40.48	3.84	13.51	1760, 1610, 1520
45	D	2	$C_{23}H_{20}N_8O_5S_2 \cdot 5H_2O$	42.99	4.71	17.44	42.82	4.39	16.98	2250, 1770, 1610
46	D	2	$C_{24}H_{22}N_8O_5S_2 \cdot 5H_2O$	43.90	4.91	17.06	43.66	4.71	17.20	2250, 1770, 1670
47	D	7	$C_{23}H_{19}FN_8O_5S_2 \cdot 3.5H_2O$	43.60	4.14	17.68	43.42	3.94	17.42	2250, 1760, 1610
48	D	3	$C_{23}H_{19}ClN_8O_5S_2 \cdot 3.5H_2O$	42.50	4.03	17.24	42.54	3.93	16.97	2250, 1770, 1650
49	E	1	$C_{25}H_{21}H_8NaO_7S_2 \cdot 5H_2O$	41.55	4.32	15.51	41.47	4.16	15.30	2250, 1780, 1610
50	D	5	$C_{23}H_{20}N_8O_5S_2 \cdot 3H_2O$	45.54	4.32	18.47	45.33	4.44	17.76	2240, 1770, 1670
51	E	3	$C_{25}H_{21}N_8NaO_7S_2 \cdot 5H_2O$	41.55	4.32	15.51	41.84	4.14	15.39	2240, 1765, 1670
52	D	9	$C_{23}H_{22}N_8O_6S_2 \cdot 4H_2O$	40.95	4.48	16.61	40.59	4.31	16.35	1770, 1680, 1610
53	D	2	$C_{22}H_{20}FN_7O_5S_2 \cdot 4H_2O$	42.78	4.57	15.88	42.53	4.30	15.39	1765, 1660, 1605

Table 8. ^{1}H NMR data for 7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylates (**1**~**20**).

Compound No.	Solvent[a]	Chemical shift δ (J=Hz)								
		Cephem nuclei				CONH	7-Acyl		R_1	3′-Imidazo[1,2-*a*]pyridinium residue
		2-CH_2 ABq (18)	3-CH_2 ABq (14)	6-H d (5)	7-H dd(5, 8)	d (8)	5-H (s)	NH_2 (s)		
1	a	2.95, 3.44	5.27, 5.47	4.99	5.59	9.46	6.68	7.16	3.80 (s)	7.4~7.6 (m), 7.85~8.15 (m), 8.4~8.9 (m), 8.9 (d, 7)
2	a	3.00, 3.45	5.28, 5.48	5.01	5.63	9.42	6.66	7.15	1.19 (t, 7), 4.06 (q, 7)	7.40~7.64 (m), 7.86~8.10(m), 8.36~8.70 (m), 8.88~9.00 (d, 7)
3	a	2.97, 3.37	5.27, 5.45	4.99	5.61	9.40	6.65	7.13	0.86 (t, 7), 1.36~1.80 (m), 3.96 (t, 7)	7.35~7.66 (m), 7.84~8.14 (m), 8.30~8.76 (m), 8.80~9.05 (m)
4	a	2.96, 3.43	5.29, 5.48	4.98	5.60	9.39	6.64	7.11	0.84 (t, 7), 1.1~1.8 (m), 4.00 (t, 7)	7.4~7.6 (m), 7.84~8.10 (m), 8.35~8.87 (m), 8.88~9.02 (m)
5	a	2.92, 3.43	5.25, 5.44	4.98	5.60	9.38	6.63	7.10	0.78 (t, 7), 1.0~1.7 (m), 3.98 (t, 7)	7.36~7.60 (m), 7.80~8.10 (m), 8.30~8.86 (m), 8.84~9.00 (m)
6	a	3.02, 3.30	5.20, 5.44	5.06	5.69	9.35	6.68	7.20	1.30~1.90 (m), 4.80 (m)	7.46~7.60 (m), 7.85~7.90 (m), 8.22~8.70 (m), 8.90 (d, 7)
7	a	2.95 —	5.28, 5.46	4.99	5.62	9.40	6.64	7.12	0.1~0.6 (m), 0.7~1.3 (m), 3.84 (d, 7)	7.30~7.60 (m), 7.86~8.20 (m), 8.20~8.80 (m), 8.80~9.02 (m)
8	c	3.00, 3.50	5.40, (s)	5.05	5.70 (d, 5)	—	6.73	—	4.60 (d, 5), 6.10~6.80 (m)	7.50~7.60 (m), 7.90~8.10 (m), 8.30~8.46 (m), 8.83 (d, 6)

9	a	3.06 —	— —	5.00	5.64	9.58	6.74	7.20	5.22～5.56 (m)	7.50～7.64 (m), 7.86～8.10 (m), 8.34～8.60 (m), 8.92 (d, 6)
10	a	2.91 —	5.26, 5.48	4.99	5.62	9.55	6.67	7.13	5.09 (s), 7.00～7.66 (m)	7.88～8.20 (m), 8.30～8.78 (m), 8.82～9.04 (m)
11	a	2.96, 3.43	5.2～ 5.6 (m)	5.00	5.61	9.50	6.70	7.16	4.0～4.2 (m), 4.2～4.5 (m), 4.7～5.0 (m)	7.4～7.7 (m), 7.8～8.2 (m), 8.3～8.8 (m), 8.97 (d, 7)
12	a	2.98, 3.43	5.25, 5.47	5.00	5.62	9.45	6.74	7.16	3.7～3.9 (m), 4.1～4.4 (m)	7.4～7.6 (m), 7.9～8.2 (m), 8.3～8.8 (m), 8.93 (d, 7)
13	a	2.97, 3.34	5.26, 5.46 (m)	4.98	5.60	9.36	6.67	7.15	3.44～3.72 (m), 4.02 (t, 6)	7.36～7.60 (m), 7.80～8.12 (m), 8.30～8.76 (m), 8.84～9.04 (m)
14	a	3.00, 3.46	5.29, 5.47	5.03	5.64	9.43	6.69	7.15	3.24 (s), 4.13 (t, 7)	7.38～7.64 (m), 7.86～8.12 (m), 8.30～8.72 (m), 8.82～9.04 (m)
15	a	3.00, 3.44	5.28, 5.47	5.02	5.66	9.70	6.78	7.15	4.36 (s)	7.00～7.60 (m), 7.86～8.10 (m), 8.28～8.70 (m), 8.86～9.00 (m)
16	a	3.02, 3.42	5.2～ 5.3 (m)	5.01	5.68	9.58	6.71	7.21	1.36 (br), 6.7～7.1 (m)	7.4～7.6 (m), 7.8～8.1 (m), 8.3～8.7 (m), 8.8～9.0 (m)
17	c	3.03, 3.45	5.33, (s)	5.03 (d, 5)	5.66	—	6.80	—	4.30 (s)	7.46～7.609 (m), 7.95～8.10 (m), 8.30～8.50 (m), 8.86 (d, 5)
18	c	3.10, 3.55	5.43, (s)	5.06 (d, 5)	5.75	—	6.73	—	1.50 (s)	7.45～7.65 (m), 7.96～8.15 (m), 8.40～8.55 (m), 8.96 (d, 8)
19	a	3.01, 3.38	5.2～ 5.5 (m)	4.96, 5.00	5.55, 5.84	11.56, 11.71	6.72, 6.78	7.12	1.32 (d, 7), 4.25～4.56 (m)	7.36～7.60 (m), 7.76～8.10 (m), 8.25～8.65 (m), 8.85～9.05 (m)
20	a	3.02	5.18～ 5.75 (m)	4.96, 5.00	5.55	11.60～ 12.00	6.71, 6.80	7.11	0.90 (t, 7), 0.92 (t, 7), 1.50～1.95 (m)	4.00～4.34 (m), 7.35～7.65 (m), 7.75～8.15 (m)

[a] a: DMSO-d_6, b: D_2O, c: DMSO-d_6+D_2O.

Table 9. ^{1}H NMR data for 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-methoxyiminoacetamido]-3-(imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylates (**21**~**41**).

Compound No.	Solvent[a]	Chemical shift δ (J=Hz)								
		Cephem nuclei				CONH	7-Acyl		R_1	3-Imidazo[1,2-*a*]pyridinium residue
		2-CH_2 ABq (18)	3-CH_2 ABq (14)	6-H d (5)	7-H dd (5, 8)	d (8)	5-H (s)	NH_2 (s)	(s)	
21	c	3.01, 3.34	5.2~5.5 (m)	4.98	5.60	—	6.71	—	3.80	7.30~7.70 (m), 7.95~8.28 (m), 8.68~9.05 (m)
22	a	3.02, 3.29	6.07, 6.25	4.95	5.56	9.45	6.67	7.15	3.80	7.3~7.6 (m), 7.72~8.80 (m), 8.44 (s), 8.78~9.00 (m)
23	a	2.96, 3.37	5.46~5.85 (m)	4.99	5.60	9.47	6.67	7.14	3.78	1.39 (t, 7), 4.48 (q, 7), 7.50~7.75 (m), 8.00~8.26 (m), 8.80~9.05 (m), 9.14 (s), 9.20~9.38 (m)
24	a	—	5.06 (br s)	5.19	5.65	9.53	6.72	7.16	3.83	2.90 (s), 7.00~7.25 (m), 7.27~7.52 (m), 7.60~7.72 (m), 7.93 (s), 8.82~9.00 (m)
25	a	3.01, 3.45	5.25, 5.51	4.99	5.60	9.45	6.68	7.15	3.79	4.70 (s), 7.50~7.78 (m), 7.95~8.25 (m), 8.6~9.0 (m)
26	a	3.08, 3.49	5.20~5.58 (m)	4.99	—	9.47	6.69	7.15	3.79	7.51 (br), 7.51~7.76 (m), 8.00~8.25 (m), 8.80~9.00 (m), 9.17 (s), 9.75 (d, 7)
27	a	3.02, 3.47	5.20~5.79 (m)	4.99	—	9.46	6.63	7.14	3.79	7.62~7.84 (m), 8.10~8.45 (m), 8.90~9.14 (m), 9.50 (s)
28	a	2.94, 3.44	5.37, 5.50	4.99	5.60	9.45	6.68	7.15	3.79	2.77 (s), 7.25~7.50 (m), 7.7~8.1 (m), 8.28~8.68 (m)
29	a	2.96, 3.45	5.24, 5.44	4.95	5.61	9.46	6.68	7.12	3.80	4.25 (s), 6.9~7.3 (m), 7.90~8.35 (m), 8.40~8.62 (m)

30	a	3.16 —	5.27, 5.49	4.99	5.61	9.46	6.68	7.14	3.80	2.83 (s), 7.32～7.58 (m), 7.78～8.12 (m), 8.34～8.36 (m), 8.40～8.72 (m)
31	a	2.97, 3.40	5.37, 5.54	4.90	5.60	9.46	6.68	7.14	3.79	7.62～8.18 (m), 8.40～8.86 (m)
32	a	2.95, 3.43	5.20, 5.41	4.97	5.54	9.45	6.68	7.14	3.78	2.41 (s), 7.70～7.96 (m), 8.20～8.65 (m), 8.72 (br)
33	c	2.90, 3.43 (br)	5.30	4.93	5.55	—	6.60	—	3.75	8.15～8.50 (m), 9.30 (s)
34	a	3.12, 3.58	5.10～ 5.40 (m)	5.00	5.71	9.25	6.57	7.20	3.78	8.0～8.7 (m), 9.45 (br)
35	a	2.95 —	5.23, 5.60	4.99	5.61	9.47	6.68	7.14	3.78	7.49～9.33 (m)
36	a	2.96, 3.34	5.23, 5.50	4.98	5.60	9.45	6.67	7.12	3.79	8.0～8.2 (m), 8.34 (br), 8.58 (br), 8.78 (d, 10), 9.28 (s)
37	a	2.95, 3.31	5.10～ 5.50 (m)	4.98	5.60	9.42	6.67	7.12	3.79	8.04～8.44 (m), 8.48～8.81 (m), 9.32 (s)
38	a	2.97 —	5.27, 5.53	5.00	5.61	9.46	6.63	7.14	3.79	8.25～8.55 (m), 8.65～9.00 (m), 9.67 (s)
39	a	3.11, 3.49 (br)	5.43	5.01	5.63	9.48	6.69	7.15	3.80	2.80 (s), 7.37 (t, 7), 7.73 (d, 7), 8.38 (d, 2), 8.58 (d, 2), 8.64～8.97 (m)
40	a	2.93, 3.31	5.18, 5.44	4.96	5.59	9.43	6.70	7.13	3.80	5.47 (s), 7.2～7.7 (m), 8.17 (d, 2), 8.50 (d, 7), 8.79 (d, 2)
41	b	3.29, 3.61	5.31, 5.65	5.22	5.84	—	7.27	—	3.98	7.27～8.60 (m)

[a] a: DMSO-d_6, b: D_2O, c: DMSO-d_6+D_2O.

Table 10. ^{1}H NMR data for 7β-[2-(2-aminothiazol-4-yl)-2(*Z*)-alkoxyiminoacetamido]-3-(substituted imidazo[1,2-*a*]pyridinium-1-yl)methyl-3-cephem-4-carboxylates (**42**~**53**).

Compound No.	Solvent[a]	Chemical shift (J=Hz)								
		Cephem nuclei				CONH	7-Acyl		R_1	3-Imidazo[1,2-*a*]pyridinium residue
		2-CH_2 ABq (18)	3-CH_2 ABq (14)	6-H d (5)	7-H dd (5, 8)	d (8)	5-H (s)	NH_2 (s)		
42	a	3.00, 3.37	5.27, 5.50	5.01	5.63	9.43	6.67	7.16	1.19 (t, 7), 4.06 (q, 7)	8.00~8.19 (m), 8.26~8.44 (m), 8.25~8.64 (m), 8.66~8.86 (m)
43	a	2.95, 3.20	5.46 —	5.06	5.43	9.55	6.73	7.20	4.00~4.25 (m), 4.30~4.54 (m), 4.65~5.01 (m)	8.10 (d, 9), 8.30 (s), 8.60 (s), 8.76 (d, 9), 9.30 (s)
44	a	3.01 —	5.40, (br)	4.97	5.67	11.45	6.67	7.10	1.42 (s)	7.96~8.16 (m), 8.30~8.80 (m), 9.32 (s)
45	a	2.99, 3.44	5.28, 5.53	5.01	5.64	9.42	6.66	7.14	1.18 (t, 7), 4.05 (q, 7)	8.2~9.0 (m), 9.77 (br)
46	a	2.98, 3.32	5.25, 5.52	5.00	5.65	9.40	6.65	7.12	0.86 (t, 7), 1.35~1.80 (m), 3.96 (t, 7)	8.20~8.55 (m), 8.6~8.75 (m), 8.80~9.00 (m), 9.74
47	a	2.99, 3.62	5.28, 5.54	5.02	5.64	9.52	6.71	7.17	4.0~4.2 (m), 4.2~4.6 (m), 4.4~5.0 (m)	8.2~9.0 (m), 9.77 (br)
48	a	2.99, 3.47	5.12, 5.27	5.02	5.64	9.50	6.72	7.19	3.6~3.9 (m), 4.1~4.4 (m)	8.2~9.0 (m), 9.78 (br)
49	a	3.02, 3.71	5.2~ 5.5 (m)	4.99	5.68	11.44	6.68	7.10	1.38 (s), 1.42	8.2~8.8 (m), 9.81 (br)
50	a	3.03, 3.47	5.32, 5.59	5.00	5.64	9.43	6.66	7.14	1.19 (t, 7), 4.05 (q, 7)	7.64~7.86 (m), 8.17~8.40 (m), 8.90~9.15 (m), 9.50 (s)
51	a	3.12, 3.49 (br)	5.40	5.01	5.71	—	6.73	7.15	1.40 (br)	7.55~7.90 (m), 8.00~8.80 (m), 9.00 (s)
52	a	3.04, 3.48	5.30, 5.52	5.02	5.64	9.44	6.67	7.15	1.18 (t, 7), 4.05 (q, 7)	7.15 (br), 7.5~8.2 (m), 8.2~8.9 (m), 9.60 (br)
53	a	— —	5.15, 5.42	5.01	5.66	9.43	6.66	7.15	1.17 (t, 7), 4.05 (q, 7)	7.33~8.93 (m)

[a] a: DMSO-d_6, b: D_2O, c: DMSO-d_6+D_2O.

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